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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Zohar H. Yakhini

Serial No.: 09/938,937

Filed: August 24, 2001

Confirmation No.: 2672

Group Art Unit: 1634

Examiner: Sisson, Bradley L.

Docket No. 10003516-1
(50113-1100)

For: Use of Unstructured Nucleic Acids in Assaying Nucleic Acid Molecules

DECLARATION OF JOEL MYERSON PURSUANT TO 37 C.F.R. §1.132

Mail Stop – AF
Commissioner for Patents
Post Office Box 1450
Alexandria, Virginia 22313-1450

Sir,

I, **Joel Myerson**, hereby declare that:

Education and Experience

1. The invention embodied in the above-identified patent application is directed to the use of Unstructured Nucleic Acids in Assaying Nucleic Acid Molecules

2. I am an employee of Agilent Technologies, Inc. (the assignee of the above-referenced patent application).

3. I am a co-inventor of the above-identified patent application.

4. I graduated from State University of New York, Buffalo, with a Bachelor of Science (1975), and from University of California, Berkeley, with a Ph.D. in Chemistry (1980).

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5. Since graduating with my Ph.D., I have been involved in a variety of pursuits related to the field of genomics, DNA synthesis, and hybridization assays. I have been employed at Agilent Technologies for almost 22 years, during which time I have, as inventor or coinventor, received numerous United States patents, and filed numerous applications, relating to these fields. These issued patents include 6,858,720 (Method of synthesizing polynucleotides using ionic liquids), 6,852,850 (Use of ionic liquids for fabrication of polynucleotide arrays), 6,743,585 (Methods for preparing conjugates), 6,716,634 (Increasing ionization efficiency in mass spectrometry), 6,689,568 (Capture arrays using polypeptide capture agents), 6,218,118 (Method and mixture reagents for analyzing the nucleotide sequence of nucleic acids by mass spectrometry). Published United States patent applications related to these fields include 20060210997 (Composition and method for array hybridization), 20040248104 (Methods and reagents for profiling quantities of nucleic acids), 20040219532 (Internal references measurements), 20040185453 (Affinity based methods for separating homologous parental genetic material and uses thereof), 20030211474 (Use of unstructured nucleic acids in assaying nucleic acid molecules), 20030022150 (Methods for detecting a target molecule), 20020182601 (Method and reagents for analyzing the nucleotide sequence of nucleic acids).

6. Through my education and work at Agilent Technologies, Inc. I have gained extensive experience in the field of genomics, including synthesizing and assaying target molecules.

The Office Action and Presently Pending Claims

7. I am advised that the United States Patent and Trademark Office (USPTO) has rejected one or more independent claims presently pending in the above-identified patent application under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement and 35 U.S.C. § 112, first paragraph, as allegedly being indefinite.

8. I have reviewed the pending Office Action from the USPTO and the specification and claims of the presently-pending application. Claim 10 is directed to a method of assaying target nucleic acid molecules by tagging and sorting the target molecules with a universal array,

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comprising the steps of:

a) providing a first plurality of nucleic acids, wherein the first plurality of nucleic acids is immobilized on a surface such that different sequences of the first plurality of nucleic acids can be differentiated by location, wherein the nucleic acid at each location has a different nucleotide sequence than nucleic acids at other locations;

b) providing a second plurality of nucleic acids, wherein the nucleotide sequence of each nucleic acid of the second plurality is known and comprises a first region and a second region, wherein each first region of each nucleic acid of the second plurality has a different nucleotide sequence from other first regions of other nucleic acids of the second plurality, wherein each first region of nucleic acids of the second plurality is complementary to a nucleotide sequence of nucleic acids of the first plurality, wherein at least one second region of the nucleic acids in the second plurality is complementary to a target nucleic acid in a biological target, wherein each nucleic acid of the first plurality and each second region of each nucleic acid of the second plurality comprises unstructured nucleotides such that the second region has a reduced ability to hybridize to a first nucleic acid of the first plurality having a complementary nucleotide sequence without reducing the ability of the second region of each nucleic acid of the second plurality to hybridize to a complementary nucleic acid molecule in a biological target;

c) providing a biological target containing nucleic acids to be analyzed;

d) contacting the biological target with the second plurality of nucleic acids under conditions that permit hybridization of complementary nucleotide sequences between the target nucleic acid molecules and the second region of nucleic acids of the second plurality;

e) contacting the second plurality of nucleic acids with the first plurality of nucleic acids under hybridization conditions;

f) detecting nucleic acids in the biological target that have hybridized to a nucleic acid of the second plurality by detecting a signal of a label that is part of the nucleic acids of the biological target;

g) determining a location of the detectable signal of the label on the surface; and

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h) determining the nucleotide sequence of the nucleic acid in the biological target that has hybridized to a nucleic acid of the second plurality by correlating the location of the signal to the nucleotide sequence.

9. I understand that the Office Action takes the position that the claimed method does not provide for any means to correlate any one position or location of the surface with any specific nucleotide sequence, be it that associated with that of a member of the first or second plurality, or with that of the biological target. The Office Action alleges that in the method of claim 10 one could well have hundreds of thousands of different members of a first plurality being immobilized to a surface of a support, and that equal or larger numbers of second plurality members and/or biological target members are in turn bound to the same surface through their interaction with members of the first plurality. The Office Action argues that with there being no known relationship between a specific nucleotide sequence, one is left solving for the values of three unknowns without having even one known entity.

10. I understand that the Office Action also takes the position that claim 10 is indefinite with respect to what constitutes the metes and bounds of a "universal array".

Discussion

11. Upon information and belief, I submit that one skilled in the art of genomics, such as myself, at the time the application was filed would understand what is meant by the term "universal array" and the fundamental concepts of how a universal array functions. For example, the specification itself states the following: "[a]n alternative array-based method of analyzing nucleic acids has been described by several groups (Brenner USP 5,604,097; Morris et al. EP 97302313), and uses a universal spatially addressable array." *Specification* at p. 21, lines 18-20 (emphasis added).

12. Furthermore, a brief perusal of issued patents prior to the filing of the instant application reveals that universal arrays were known and described in the art already. In the instant case, there are at least two patent references that discuss and describe what universal arrays are, and

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how they function with the use of a first plurality and a second plurality of nucleic acids in addition to the target molecules. For example, U.S. Patent No. 6,268,147 issued to Beattie *et al.* on July 31, 2001 discusses and illustrates universal arrays at *e.g.*, FIGS. 1, 14A, 14B, 15A, 15B, and col. 35, line 60 – col. 35, line 67. By way of additional example, U.S. Patent No. 6,083,763 issued to Balch on July 4, 2000 also discusses universal arrays throughout, *e.g.*, at FIG. 5a and correlating discussion.

13. With respect to the issue as to whether the claims enable one skilled in the art at the time the application was filed to practice the claims, claim 10 recites the following: "different sequences of the first plurality of nucleic acids can be differentiated by location" and "wherein the nucleotide sequence of each nucleic acid of the second plurality is known." (emphasis added). The subject matter of the claim would enable one to practice the method when read light of the specification for the recited language. The specification at pp. 21-23 discussed a universally spatially addressable array and how one works. For example, the specification states the following:

> To analyze and detect nucleic acids in a sample, methods using a fixed array design rely on the use of an intermediate nucleic acid molecule which hybridizes to a target nucleic acid molecule with one region ("anti-target") and also hybridizes to an oligonucleotide probe on the fixed array with another region ("tag"). The intermediary molecules therefore contain two domains that perform the two functions of 1) binding to a target molecule and 2) sorting the target molecules by binding to a spatially addressed probe ("anti-tag") on the fixed array. These two steps can be performed, in any order, separately or simultaneously. Thus the fixed array of oligonucleotides is designed to provide a substrate for sorting target molecules.

Specification at page 22, lines 1-9. In addition, the specification explains the assay system in the following example:

> For example, in a six nucleotide region of an array bound oligonucleotide comprising A, T, G, and C, only 4096 sequences are possible for that six nucleotide region of the oligonucleotide. Therefore, in the universal tag system comprising anti-target sequences that are designed to assay a high number of target sequences, there is a likelihood that anti-target nucleic acids comprise sequences complementary to regions of the array-bound oligonucleotide. In particular, simulation studies conducted using uniformly drawn single nucleotide polymorphisms (SNPs; e.g amplicons of length 41 and a uniform middle base bi-allelic polymorphism) and multiplexing optimization heuristics show that only 25-30% of the sites on a universal fixed array are accessible when performing

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specific genotyping assays which interrogate 1000 samples.

Specification at page 23, lines 13-23.

14. Because the specification teaches how different sequences of the first plurality can be differentiated by location, and because the sequence of each acid of the second plurality is known, when the nucleic acids of the second plurality have hybridized to a target with a signal, and also to a first plurality, the sequence of the target can be determined.

15. Based on the foregoing, including the understood definition and functionality of a universal array, and upon information and belief, I submit that one of skill in the art, upon a review of the instant application, could reasonably/easily assay target nucleic acid molecules by tagging and sorting the target molecules with a universal array as recited in claim 10.

Conclusion

16. Based on the foregoing, and upon information and belief, I further submit that one skilled in the art of genomics, such as myself, a the time the application was filed would understand from a review of the instant application how to perform the methods recited in claim 10, and claims 11-14 which depend therefrom, without undue experimentation.

17. In addition, based on the foregoing, one skilled in the art would understand the meaning of the term "universal array" and how a universal array functions.

I hereby declare that all statements made herein are of my own knowledge are true and that all statements are made on information and belief and are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the

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United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

18 October 2006
Date

Joel Myerson

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